An Evaluation of Infertility Factors

EDMUND W. OVERSTREET, M.D., *San Francisco*

DURING the war our study and treatment of infertile couples was much interfered with. So many people changed residence so often that systematic observation and therapy was almost impossible. Moreover, the greatly increased birth rate tended to focus the attention of the obstetrician-gynecologist more on the problem of coping with this reproductivity than on that of enhancing it. But now that the youth of this country is again free to undertake familial responsibilities, our offices and clinics are increasingly besieged by barren couples. This is, therefore, an opportune time for us to take stock of our knowledge in this field and to re-evaluate our techniques for the study and treatment of infertility.

Experienced workers in the field of infertility have made various classifications of the factors which play an etiologic role. In general they are agreed on five principal groups of such factors. These are listed, not in the order of their importance, but in the order of their consideration here.

1. The Coital Factor
2. The Male Factor
3. The Tubal Factor
4. The Female Endocrine Factor
5. The Cervical (and Vaginal) Factor

For a more extensive classification of these groups—correlated, moreover, with diagnostic and therapeutic procedures—attention is called to the excellent one which forms the basis of the brief paper by Page and Page[6] on "An Outline For The Office Investigation of Sterility."

Each student of infertility accords a certain significance and emphasis to each major group of factors. The various opinions are often widely divergent. Our aim will be to cast a little light on the relative importance of these factors, and to attempt to point out where there has been overemphasis and where there may have been insufficient attention. There is not space for even an adequate discussion of specific diagnostic and therapeutic methods, but certain of them have been selected for mention because of common misconceptions concerning them.

THE COITAL FACTOR

Let us touch only briefly on this factor. That is not, however, to underestimate its importance. In general, a simple but searching coital history plus a post-coital, Hühner test will give us an adequate knowledge of the role it plays in the infertility of any couple. But we have all had the painful experience of being deceived by an occasional wife who at the outset has given a history of what seemed to be satisfactory sex adjustment, only to discover on later and deeper probing that male impotence, dyspareunia, infrequent coitus, or unannounced coital techniques played a real part in the couple's infertility.

It is in the relationships of this factor, also, that we have made a beginning in the direction of giving due weight to the psychosomatic factor in infertile couples. What part satisfactory sex adjustment plays, for example, in the physiology of reproductive tract secretions is as yet obscure, but we begin to suspect that we cannot ignore it in carrying out a complete infertility study. The determination of the degree and extent of psychic influence on the reproductive soma represents an almost totally unexplored field of which we are just becoming aware, one which may repay us well for our study of it.

We all know, on the other hand, how frequently pregnancy occurs as a result of the most inept coital techniques. The following factors in our list are certainly much more significant in the problem of infertility.

THE MALE FACTOR

This factor in childless couple does not even now receive the attention it deserves. This is true in spite of the fact that extensive study by specialized workers has vastly increased our understanding of it. Moreover, there is surprisingly good agreement in the literature on how frequently it is the paramount defect in infertile couples. Almost all studies place its incidence in this respect at between 30 and 40 per cent. The casual physician, called upon to explain infertility, unfortunately is not fully aware of this possibility.

That *the male factor* is widely ignored, was forcibly brought home to many of us during army service as we moved from one station to another in this country, attempting to do a small amount of infertility work on army dependents in addition to other duties. It was heartbreaking to encounter the amazing number of young wives who had undergone fairly extensive sterility studies—even major operative treatment—without a spermanalysis ever having been required of their husbands. It was equally discouraging to find that many of these wives thought that their husbands had had adequate semen analysis—when in reality all that had been done was to glance quickly through a microscope to see if motile spermatozoa were present in the semen.

It is true that our present methods of spermanalysis leave much to be desired. They have been likened to trying to determine the character of a person by looking at him from the top of a tall building as he circulates in a mob of people on the street below. Actually, of course, we *can* tell a good deal about individuals in a mob by observing the behavior of the mob itself. The same is true of spermatozoa. By correlating the characteristics of the mob of sperma-

Presented before the section on Obstetrics and Gynecology at the 76th Annual Session of the California Medical Association, Los Angeles, May 1, 1947.

From the Division of Obstetrics and Gynecology, University of California Medical School, San Francisco, California.

tozoa with actual male fertility we reach an indirect estimate of the fertility of the individual fertilizing sperm. The more carefully we observe the sperm mob —the semen, that is—the more satisfactory the correlation becomes. Authorities now agree that simply determining the presence of motile spermatozoa in semen is not a satisfactory criterion of fertility—so the brief glance down the microscope is no longer enough. A minimum analysis should certainly include:

1. The physical characteristics of the semen: Volume, viscosity, and presence of abnormal contents.
2. A careful sperm count.
3. A properly stained differential count of abnormal forms.
4. An accurate estimate of percent of motile sperms at various intervals of a 24-hour period (at room temperature).

Such a semen analysis may well eliminate a long and fruitless search for infertility factors in the wife and lead instead to simple treatment of the husband with early resultant pregnancy. Certainly there is no need to emphasize this important point for the present reader.

FEMALE INFERTILITY FACTORS

We come now to discussion of the etiologic factors present in the female. Table 1 presents a collection from the recent literature of incidence figures for the three important groups of factors. It serves to emphasize the areas of certainty and uncertainty in our present knowledge.

THE TUBAL FACTOR

Note that the reports on incidence of *the tubal factor* in infertile women are rather consistent. It plays the major role in 40 to 50 per cent of cases. Thanks to the intensive work of such men as Rubin and Cary the physiology and pathology of this factor are quite well understood. The techniques for studying and treating tubal dysfunction have been so well presented in recent publications[3,9,11] that discussion of them here is not necessary.

One word of warning however should be said. Too many physicians make a final decision regarding the tubal status after only a single tubal insufflation or hysterosalpingogram. The relative merits of the two methods would be too lengthy a topic for discussion here; but it has been well demonstrated by Sharman[9] that a single test with *either* method is subject to about a 10 per cent error. While this error can only be eliminated by repeated tests it can often be reduced by the use of anesthesia, a sedative, or an antispasmodic when the test is performed.

TABLE I

INCIDENCE OF ETIOLOGIC FACTORS IN FEMALE INFERTILITY

AUTHOR	NUMBER OF CASES	CERVICAL FACTOR		TUBAL FACTOR	ENDOCRINE FACTOR
		DEEMED PRESENT	ACTUAL LESIONS		
MAZER & ISRAEL[8]	695	32%		55%	35%
NICODEMUS & RITMILLER[11]	76		4%	50%	69%
WINSON[26]	257	38%		54%	52%
SIEGLER[21]	410	38%	32%	51%	59%
GUERRERO[2]	438	11%		31%	16%
McLANE[9]	372	23%		13%	14%+
SHARMAN[19]	500			38%	
THIS SERIES	50		70%		

TABLE II

INCIDENCE OF OCCASIONAL ANOVULATION IN INFERTILE FEMALES

AUTHOR	NUMBER OF CASES	METHOD OF DETERMINATION	INCIDENCE OF ANOVULATION
KOTZ & PARKER[6]	47	ENDOMETRIAL BIOPSY	36%
ROCK, BARTLETT, & MATSON[17]	392	ENDOMETRIAL BIOPSY	9%
NOVAK[12]	39	ENDOMETRIAL BIOPSY	49%
JEFFCOATE[5]	63	ENDOMETRIAL BIOPSY	25%
EFFKEMANN[1]	81	ENDOMETRIAL BIOPSY	14%
HALBRECHT[3]	130	BASAL BODY TEMPERATURE	12%
MAZER & ISRAEL[8]	695	BASAL BODY TEMPERATURE	15%
WINSON[26]	257	BASAL BODY TEMPERATURE	35%
McLANE[9]	372	BASAL BODY TEMPERATURE	14%
SHARMAN[19]	500	BASAL BODY TEMPERATURE	6%
ZONDEK[27]	2000	MIXED	11%
COMBINED SERIES	4576	ALL	13.3%

THE FEMALE ENDOCRINE FACTOR

One aspect of *the female endocrine factor* that has received great attention in recent years is the study of defective oogenesis by the determination of anovulatory menstrual cycles—or, if you will, pseudomenstrual cycles. Many workers have placed great emphasis upon absence of ovulation as an infertility factor, and have devoted endless time to devising methods for the hoped-for stimulation of ovulation. But *is* this an important factor in female infertility in general?

Morton and Hayden,[4] gave us a good baseline for the consideration of this problem. They showed, by means of endometrial biopsies, that in apparently normal women, having normal menses, under the age of 40, who had had one or more pregnancies, the incidence of one or more anovulatory cycles over a moderate period of time was about 7 per cent. In similar normal women, not taking the question of previous pregnancy into account, they found the incidence of occasional anovulatory cycles to be about 12 per cent.

What is the incidence in infertile women?

Table 2 presents a collection of figures from the literature. These figures represent the findings of various investigators in terms of what *they* considered to be a *significant degree* of anovulation. Consequently, too much weight cannot be given to them, because the criteria for a significant degree of anovulation are not the same for different workers. Indeed, it is probable that all menstruating women at one time or another have one or more anovulatory

cycles. At just what point such cycles become frequent enough to be a factor in infertility is difficult to decide, and many of the authors in the literature do not state their criteria for making such a decision. The figures of Table 2, however, represent the decisions of respected workers in this field, and as such should carry a certain weight. As quoted, each figure represents the percentage of infertile women in whom it was felt that anovulatory cycles were frequent enough to play a major role in their infertility.

Note the marked divergence of opinion regarding the incidence of significant anovulation in infertile women. One series runs as high as 50 per cent, another as low as 6 per cent. Whether the difference is due to sampling error or to interpretation of the methods used for determination of ovulation is difficult to say; doubtless both factors play a part. If, as seems likely, the former is the more important factor, we can get a better—though still very rough—idea of the true incidence by properly combining these series, using, that is, each percentage figure applied to the corresponding number of cases.

This gives us a total of 4,576 infertility cases with an overall incidence of anovulation of 13.3 per cent. While this figure is twice that for normal women who have borne children, 7 per cent, it is not significantly higher than that for normal women without regard to pregnancy, 12 per cent.

Yet an inordinate amount of attention is being directed to the treatment of this factor in infertile women. So far we have not been able to devise a proven method for direct, immediate stimulation of ovulation. Perhaps this very frustration entices us into redoubled efforts to solve the problem. But should the quest for such a method overshadow study of the other infertility factors?

There is another aspect of *the female endocrine factor* on which we might well dwell for a moment. In certain infertile women we tend to make a rather doubtful assumption. If other sterility factors have been ruled out and if the woman manifests a mild endocrine dysfunction—pituitary, thyroid or ovarian—we are likely to conclude that the endocrine dysfunction is the *cause* of the infertility. In the case of thyroid dysfunction the evidence for this causal relationship is rather good. In the case of pituitary and ovarian dysfunction the evidence is very tenuous. Where such an endocrine upset can be directly related to the occurrence of frequent anovulatory cycles—and where correction of the upset restores ovulation—we are on safe ground. But where ovulation is not in question, to assume that mild pituitary or ovarian dysfunction means the production of infertile ova is very dubious logic. Our knowledge of the physiology of the human ovum is too incomplete to support such reasoning.

What is more important is that this type of thinking may lead to a preoccupation with endocrine therapy which is out of all proportion to its importance and which may turn our attention away from the search for more likely infertility factors.

Both of the foregoing facts are, I think, implicit in the marked disagreement among various authorities regarding the incidence of *the female endocrine factor* in infertile couples. Table 1 shows this clearly.

Nevertheless, the therapeutic approach to infertility with pituitary extracts, chronionic gonadotropins, and ovarian hormones in various dosages and schedules has been labored to the point of absurdity. In conscientious and knowing hands the use of hormone therapy of this type has progressively decreased. Unfortunately, in the therapy of physicians in general its use has steadily increased. Such hormones are now frequently being given purely empirically. They are being given unjustifiably. They are being given irrationally. In some cases they are being given to the definite detriment of the patient. Even a brief comparison of reports in the literature will demonstrate that the percent of pregnancies obtained by those physicians who employ little hormone therapy other than thyroid extract is just about the same as that obtained by those who overdose their patients with all the newest products of the pharmaceutical manufacturers.

THE CERVICAL (AND VAGINAL) FACTOR

Unfortunately, dependence on hormone therapy is often at the expense of attention to the least understood but perhaps most hopeful infertility factor, *the cervical factor*. One is much concerned, for example, when it is realized how many physicians carry out prolonged infertility studies and intensive endocrine therapy without ever performing a post-coital, Hühner Test. Yet it is an indispensable aid in pointing to cervical and vaginal pathological changes of such minor degree as to be difficult of direct observational diagnosis though great enough to be a barrier to spermigration.

That such minimal pathological changes may play an important infertility role is suggested by Siegler's recent paper.[12] He presented 106 cases of infertility in whom study revealed no specific cause and usual treatment methods failed. When a pre-coital douche of Ringer-glucose solution was prescribed for use at the time of ovulation, 29 of these couples conceived. Twenty-seven per cent success is a laudable figure for any type of infertility treatment, and it is to be hoped that sampling error did not enter into it too greatly, or that previously-used treatment did not pave the way for final success. However, in our own last 50 cases of infertility three patients conceived with no treatment whatever other than the pre-coital use of Ringer-glucose solution. One of these three had been infertile for two years but became pregnant at the first ovulation with which the treatment was used.

Whether such a therapeutic result represents a direct effect on cervical and vaginal secretions or whether it represents a stimulation of slightly-below-par spermatozoa is not yet clear; doubtless both factors are involved. Moreover, we are all familiar with the fact that a small percentage of patients become fertile simply as the result of using a therapeutic douche for a short time—and the question of sperm stimulation does not enter here. In any event, present evidence suggests that the beneficial effect

of such therapy so far as secretions are concerned is exerted principally upon those of the cervix, and that artificial alteration of vaginal secretions is of minor importance. That is our reason for classifying *the vaginal factor* only parenthetically with *the cervical factor.*

It may well be that in our routine pelvic examination of infertile women we overlook mild degrees of cervical or vaginal pathological change—or that we have not yet devised adequate methods for detecting them. With regard to the latter, we should cite the important basic work on the physiology of the cervical mucus carried out by Lamar, Shettles, and Delfs[2] and its recent further development by Pommerenke.[7,13,14] Further investigations of this sort are certain to give us more adequate techniques for the study of *the cervical factor* in infertility.

Table 1 suggests how poorly understood—and perhaps how frequently overlooked—*the cervical factor* is today, for the figures reported for its incidence show great variation. To test this conjecture briefly we reviewed our last 50 cases of infertility with special attention to this factor. They were given a minute scrutiny for any evidence of even a minimal cervical or vaginal lesion. Such evidence was considered to be: visible cervicitis, cervical erosion, purulent or excessive cloudy cervical discharge, evident vaginitis, or the finding of vaginal parasites or fungi. According to these criteria, the incidence of *the cervical factor* in our small series of 50 cases was 70 per cent! As might be expected, other, sometimes more important, infertility factors were present in these patients (Page and Page,[6] studying patients from this area, found the average number of infertility factors per couple to be 2.4). But such a high incidence of cervical and vaginal lesions certainly cannot be by chance. We see nothing like it in the normal, fertile woman.

At the present time, however, even meticulous direct observation of the cervix and vagina probably will not always reveal the presence of *the cervical factor.* The Hühner Test, an immensely valuable diagnostic procedure, should never be omitted. Unfortunately, it has not been sufficiently employed and studied to bring its development to a satisfactory high point of neatness and accuracy. Its present technique is rough and gross. Aspiration or sampling of cervical mucus sometimes presents a problem in its dexterous, uncontaminated accomplishment. Methods for sampling from different levels of the cervical canal are only now in a process of development, and bid fair to provide significant findings. At present the interpretation of Hühner Test findings is not even well standardized—as is attested by disagreement between outstanding workers in the field.[8,15] Selection of the optimum time for the test, that of ovulation, is not rigidly adhered to so that the findings of many users are misleading. While it was originally felt that the test should be carried out within one to two hours after coitus, recent work suggests that more valuable information may be gained at four to six hours.

It is evident that the Hühner Test has not reached its full development. Its wider use, therefore, with refinement of its technique seems imperative; for it promises to give indispensable information about infertility factors. Many possibilities are open to those of us who will give this valuable investigative procedure its proper place in our armamentarium.

Along with our diversion of attention from *the cervical factor* our methods of treatment of cervical lesions have remained almost at a standstill. Indeed, in view of the delicate physiology of the cervix and the nicely balanced cervico-vaginal chemical relationships, one wonders whether some of our more vigorous therapeutic methods may not have left the patient more infertile than she was prior to their use. Too deep a cauterization may produce unfortunate cervical sequelae. Too extensive conization may remove too many of the essential mucus-secreting glands. Too vigorous chemical treatment may produce a chemical inflammatory reaction in the cervix which offers as much of a barrier to ascent of spermatozoa as did the original cervical lesion. We are just beginning to consider the use of our newer antibiotic and chemotherapeutic agents in the treatment of cervical and vaginal infections, and other, more delicate methods are only dimly envisioned. But unless we place proper emphasis on the importance of *the cervical factor* in infertility, the development of these methods will continue to lag.

We have all tended, in our desire to aid the oftenpitiful infertile couple, to grasp at straws in our attempts to elucidate the factors involved. The Rh factor is a case in point. Rh incompatibility has been called in question as a possible etiologic factor in infertility. Recent papers[1,5] have already shown rather convincingly that the previously-assumed role of the Rh factor in the causation of early abortion is mythical; it is even less likely that the similar assumption regarding its role in infertility is a valid one.

Rather than devote too much of our time to grasping at such straws let us return to a more searching study of familiar but poorly-understood infertility factors. Of these *the cervical factor* is perhaps the most deserving of our attention.

Discussion by PENDLETON TOMPKINS, M.D., *San Francisco*

I have been wondering in what respect the specialist in sterility possesses an advantage over the general practitioner. The difference is not in knowledge (for Dr. Overstreet has refreshed our recollection of the factors essential for reproduction), nor in equipment (for the specialist possesses no instruments not found in the office of the general practitioner excepting a curette for office endometrial biopsies and a machine for tubal insufflation). Even these two instruments may be temporarily dispensed with, for the basal temperature graph gives information regarding ovulation which is comparable to that provided by endometrial biopsy, and a uterosalpingogram is a substitute (though a poor substitute, in my opinion) for tubal insufflation. Since the specialist requires no rare knowledge and no indispensable equipment, what is the basis for his reputation? Simply this: thoroughness. He takes the time to secure a complete history, he procures blood counts, urinalyses, Wassermann tests, basal metabolism tests; he secures accurate temperature graphs and

records of coitus, and he insists upon complete sperm counts. Dr. Lewis Michelson of San Francisco, one of the eminent students of male fertility in this country, requires studies of three different specimens of semen before evaluating male fertility. He feels that a single specimen may be exceptionally good or exceptionally poor and quite unrepresentative of the normal of the individual.

The specialist in female infertility will scrutinize the cervix with a more critical eye than any other gynecologist. It does not suffice that there is no gross evidence of endocervicitis. The cervical mucus should be examined for leukocytes indicating cryptic endocervicitis. The canal should be delicately probed to discover pockets, synechiae or adhesions. These are important, not because they obstruct the passage of sperm, which are after all much smaller than a red blood cell, but because these pockets interfere with cervical drainage and are associated with abnormal cervical mucus. In every study the cervix should not only be gently probed and sounded but also should be slightly dilated. I have often wondered what part cervical dilatation has played in those cases of conception which have followed "the initial examination," an endometrial biopsy without other treatment, or a single tubal insufflation. In such cases the passage of an instrument through the canal may have been more beneficial than was recognized.

Endocrine therapy has been used in many forms and according to many schedules to stimulate ovulation or to increase the sperm count. If our present evaluations are correct the only certain effect of such therapy is to delude at least one person—the physician administering it.

REFERENCES

1. Hunt, A. B.: Rh factor in abortion, Am. J. Obst. & Gynec., 53:467 (March), 1947.

2. Lamar, J. K., Shettles, L. B., and Delfs, E.: Cyclic penetrability of human cervical mucus to spermatozoa in vitro, Am. J. Physiol., 129:234 (May), 1940.

3. Mazer, C., and Israel, S. L.: Menstrual disorders and sterility, Paul Hoeber, New York, 1946.

4. Morton, D. G., and Hayden, C. T.: Incidence of ovulation as determined by endometrial biopsy, West. J. Surg., Gynec. & Obst., 49:15 (Jan.), 1941.

5. Overstreet, E. W., Traut, H. F., Hunt, M., and Lucia, S. P.: Does Rh-Isoimmunization Cause Early Abortion?, Am. J. Obst. & Gynec., 54:235 (Aug.), 1947.

6. Page, E. W., and Page, C. W.: Outline for office investigation of sterility, Urol. and Cutan. Rev., 48:11 (Jan.), 1944.

7. Pommerenke, W. T.: Cyclic changes in physical and chemical properties of cervical mucus, Am. J. Obst. & Gynec., 52:1023 (Dec.), 1946.

8. Rock, J.: Proc. Conf. on Diagnosis in Sterility, Charles C. Thomas, Springfield, Ill., 1946, p. 234.

9. Rubin, I. C.: Uterotubal insufflation, C. V. Mosby Co., St. Louis, 1947.

10. Sharman, A.: Some recent studies and investigations in sterility, abstr., Proc. Roy. Soc. Med., 37:67 (Dec.), 1943.

11. Siegler, S. L.: Fertility in women, Lippincott, Philadelphia, 1944.

12. Siegler, S. L.: Value of physiologic substrates in sperm migration in selected cases of human infertility; observations in series of 106 patients, Am. J. Obst., 51:13 (Jan.), 1946.

13. Viergiver, E., and Pommerenke, W. T.: Measurement of cyclic variations in quantity of cervical mucus and its correlation with basal temperature, Am. J. Obst. & Gynec., 48:321 (Sept.), 1944.

14. Viergiver, E., and Pommerenke, W. T.: Cyclic variations in viscosity of cervical mucus and its correlation with amount of secretion and basal temperature, Am. J. Obst. & Gynec., 51:192 (Feb.), 1946.

15. Williams, W. W., Proc. Conf. on Diagnosis in Sterility, Charles C. Thomas, Springfield, Ill., 1046, p. 156.

Surgical Operations Upon the Aged

J. NORTON NICHOLS, M.D., *Los Angeles*

THE number of patients in the advanced age group increases with each passing year. We are told that 80 years ago, at the close of the war between the States, the average life expectancy of a baby was 40 years. Today it is 60, with the indications of a still further extension of the life span. There are in our country today approximately 10 million persons of an age of 65 or beyond, and the infant born this year, if he attains his 65th birthday, should find himself one of twenty million as old as he is or older. The care of this group enters the life of every physician, and this discussion pertains to the surgical aspect of that service.

What constitutes the "aged" patient? We have mentioned 65 as a working point, yet certainly age itself is not determined by the calendar. Circulatory deficiency, renal impairment, obesity, diabetes, and many other conditions may so alter the picture that an individual becomes older than his stated age. For clarity in this presentation it will be assumed that we are speaking of patients past 65 who are normal for age, or of those perhaps younger with unfavorable factors which bring them up to the same life expectancy. The term "surgical age" would be a good one and might well be used in each doctor's record showing his estimate of that patient as compared with an imaginary normal. Thus an individual of 60 might be tabulated as having a surgical age of 70, if in the opinion of his physician his condition was no better than the normal for the latter group. Such a classification might prove valuable in considering the advisability of elective surgical procedures.

The most common conditions contributing to a poorer-than-normal status are, in the order of this writer's prejudice, cardiovascular disease, obesity,

Read before the sections on General Practice and Anesthesiology at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.